

Water intoxication after low dose cyclophosphamide

Drs M O McCARRON, G D WRIGHT, and S D ROBERTS (Departments of Rheumatology, Royal Victoria and Musgrave Park Hospitals, Belfast) write: A syndrome of inappropriate antidiuretic hormone leading to water intoxication and death has been reported with high dose cyclophosphamide (30-50 mg/kg).¹ However, it was thought that water intoxication did not occur if cyclophosphamide was used in doses below 30 mg/kg.² We report the case of a 59 year old woman with systemic lupus erythematosus who was admitted to hospital with headache, depression, and vertigo. Current drugs were thyroxine, paroxetine, warfarin, and thioridazine. Central cerebral involvement was confirmed on magnetic resonance imaging. Analysis of urine gave normal results; serum sodium concentration was 138 mmol/l, serum potassium concentration 4.5 mmol/l, urea concentration 4.5 mmol/l, serum creatinine concentration 56 µmol/l, and creatinine clearance 64 ml/minute.

She started taking 20 mg prednisone daily and pulsed intravenous cyclophosphamide (10 mg/kg) at weekly intervals, with mesna at 0, 4, and 8 hours. Intravenous fluids were infused at 100 ml/h for 24 hours after cyclophosphamide. Within 12 hours of the second bolus she developed headache, nausea, and vomiting. She became increasingly confused and somnolent. Emergency analysis of electrolyte concentrations is shown in the table. A diagnosis of inappropriate antidiuretic hormone secretion was made in view of the hyponatraemia with an inappropriately high urine and serum osmolality. Fluid was restricted and by 48 hours the patient was fully oriented with normal serum electrolyte concentrations.

To our knowledge, life threatening water intoxication with low dose intravenous cyclophosphamide (10 mg/kg) has not been reported previously, although hyponatraemia has been induced by low dose cyclophosphamide in a patient who was also taking indomethacin.³ The mechanism of cyclophosphamide induced water intoxication is not known. Radioimmunoassay of antidiuretic hormone concentrations show no rise.⁴ Therefore, the term syndrome of inappropriate antidiuretic hormone is a misnomer. A possible mechanism is a direct effect of cyclophosphamide or a metabolite on the kidney, causing enhanced permeability of the distal tubules to water.

Awareness of the potentially life threatening complication of water

Course of electrolyte changes during intravenous pulse cyclophosphamide

	Time after second cyclophosphamide dose (h)				
	Admission	12*	24*	36*	48*
Sodium (mmol/l)	138	122	116	120	130
Potassium (mmol/l)	4.5	4.9	4.8	5.1	4.7
Urea (mmol/l)	4.5	3.1	2.9	3.6	4.9
Albumin (mmol/l)	36	30			
Calcium (mmol/l)	2.3	2.05			
Creatinine (µmol/l)	56	56			
Glucose (mmol/l)			6.2		
Osmolality (mmol/kg):					
Serum (normal range 285-290)			250	250	
Urine (normal range 250-1250)			567		

*Fluid restriction.

intoxication is imperative for medical staff treating patients with low dose intravenous cyclophosphamide.

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- 3 Webberley MJ, Murray JA. Life-threatening acute hyponatraemia induced by low dose cyclophosphamide and indomethacin. *Postgrad Med J* 1989;65:950-2.
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Potential of warfarin by interferon

Drs Y ADACHI, Y YOKOYAMA, T NANNO, and T YAMAMOTO (Kinki University School of Medicine, Osakasayama, Osaka 589, Japan) write: After giving interferon to a patient with chronic hepatitis C who had been taking warfarin, we observed increased anticoagulation, with an increased serum warfarin concentration necessitating a reduction in dose.

A 52 year old woman with a history of post-transfusion chronic hepatitis C after heart surgery in 1985 had received warfarin postoperatively. Her maintenance dose alternated between 3.5 mg and 2.5 mg daily. Investigations on admission in September 1992 showed a prothrombin time of 16.7 s (international normalised ratio 1.60), a Thrombotest (Eisai, Japan) result of 27% (international normalised ratio 1.53),¹ and serum warfarin concentration of ≤ 0.8 µg/ml. On 9 September 1992 she started taking human lymphoblastoid interferon alfa at a dose of 6.0 MU daily for 14 days, then three times a week. Although the results of other liver function tests did not change appreciably, prothrombin time increased to 20.4 s (international normalised ratio 1.99), Thrombotest results decreased to 17% (international normalised ratio 2.00), and serum warfarin concentration rose to 5.2

µg/ml after 10 days. We reduced her warfarin dose to 2.5 mg/day for 10 days, then to 2.0 mg/day. By 5 October both anticoagulation and serum warfarin concentration had returned to nearly their initial values.

Interferon does not directly affect the coagulation system.² It inhibits hepatic microsomal enzymes that metabolise drugs, however, in mice³ and humans.^{4,5} The potentiation of warfarin activity by interferon may therefore be the result of decreased drug metabolism. We have also had to decrease the dose of warfarin in four other patients, two taking interferon beta concomitantly and two taking interferon alfa-2b concomitantly. When interferon is given to patients who are receiving warfarin, the degree of anticoagulation should be carefully monitored.

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Fulminant hepatic failure induced by lamotrigine

Drs A J MAKIN, S FITT, and Professor ROGER WILLIAMS (Institute of Liver Studies, London SE5 9PJ), and Dr J S DUNCAN (National Hospital for Neurology and Neurosurgery, London WC1N 3BG) write: Although lamotrigine causes skin eruptions in 3% of cases,¹ to our knowledge, it has not been reported to cause hepatotoxicity. We report a case of fulminant hepatic

failure induced by lamotrigine.

A 22 year old woman with epilepsy was admitted with complex and secondarily generalised seizures, despite treatment with sodium valproate, carbamazepine, and vigabatrin. Valproate was reduced, vigabatrin was withdrawn, carbamazepine was changed to a slow release preparation, and treatment with lamotrigine 50 mg daily was started and increased over three weeks to 100 mg twice daily. She presented two days later with a fever of 37.5°C, a maculopapular rash, and a raised plasma aspartate aminotransferase concentration of 913 IU/l and lamotrigine was withdrawn. Over 48 hours she became encephalopathic, requiring ventilation, and her liver function deteriorated further (aspartate aminotransferase concentration 2674 IU/l, international normalised ratio 4.5). Although she developed cerebral oedema, her liver function improved until she died unexpectedly of a massive pulmonary embolus 58 days after admission.

Lamotrigine is the likely cause of the fulminant hepatic failure as there was no serological evidence of a viral hepatitis and paracetamol was not detected. A liver biopsy specimen showed acute hepatic necrosis with no evidence of chronic liver disease; although valproate and carbamazepine can both cause fulminant hepatic failure, this case had none of the characteristic features,^{2,3} and no other drug could be implicated. Lamotrigine treatment has been associated with multiorgan failure and disseminated intravascular coagulation, in which uncontrolled seizure activity was thought to cause rhabdomyolysis, which then precipitated these events.⁴ A further fatal case reported to the Committee on Safety of Medicines (personal communication) was similar to these earlier cases, but a recent report of multiorgan failure and disseminated intravascular coagulation associated with lamotrigine implicated the drug as the cause as there was no history of fitting just before admission.⁵ We suggest that these potentially fatal side effects should be considered in any patient when clinical deterioration follows instigation of lamotrigine treatment.

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